

CLAIMS

What is claimed is:

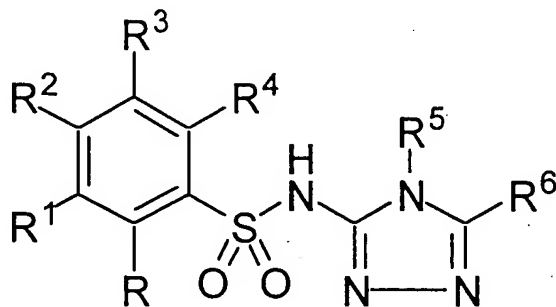
1. A method of treating a bacterial infection  
5 of a mammal, comprising administering to a mammal suffering from a bacterial infection an amount of a compound active against a bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105 sufficient to inhibit the growth of bacteria involved in said infection.

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2. The method of claim 1, wherein said bacterial infection involves a bacterial strain expressing a gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105 or a homologous gene.

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3. The method of claim 2, wherein said gene corresponds to SEQ ID NO. 60 and wherein said compound has the structure:



20

wherein

R, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are independently H, alkyl (C<sub>1</sub>-C<sub>5</sub>), or halogen;

$R^4$  is H, alkyl ( $C_1-C_5$ ), halogen, SH, or S-alkyl ( $C_1-C_3$ );

$R^5$  is H, alkyl ( $C^1-C^5$ ), or aryl ( $C_6-C_{10}$ );

$R^6$  is  $CH_2NH_2$ , alkyl ( $C_1-C_4$ ), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, or aryl  
5 ( $C_6-C_{10}$ );

or

$R^5$  and  $R^6$  together are  $-C(R^7)=C(R^8)-C(R^9)=C(R^{10})-$ ,  $-N=C(R^8)-C(R^9)=C(R^{10})-$ ,  $-C(R^7)=N-C(R^9)=C(R^{10})-$ ,  $-C(R^7)=C(R^8)-N=C(R^{10})-$ ,  
or  $-C(R^7)=C(R^8)-C(R^9)=N-$ ;

10                    wherein  $R^7$ ,  $R^8$ ,  $R^9$ , and  $R^{10}$  are independently H, alkyl ( $C_1-C_5$ ), halogen, fluoroalkyl ( $C_1-C_5$ );

or

$R^7$  and  $R^8$  together are  $-CH=CH-CH=CH-$ .

15                    4. A method of treating a bacterial infection in a mammal comprising administering to said mammal an amount of an antibacterial agent effective to reduce said infection,

                  wherein said antibacterial agent specifically inhibits  
20 a biochemical pathway requiring the expression product of a gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105, and

                  wherein inhibition of said biochemical pathway inhibits the growth of said bacterium *in vivo*.

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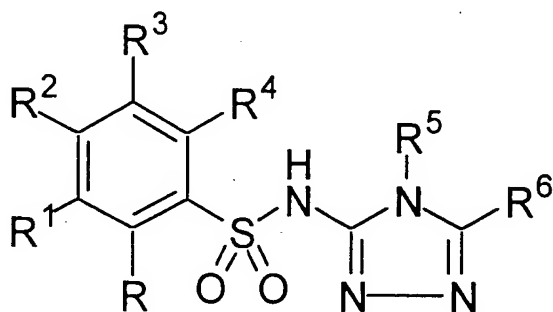
                  5. A method of inhibiting the growth of a pathogenic bacterium comprising contacting said bacterium with an antibacterial agent which specifically inhibits a

biochemical pathway requiring the expression product of a gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105,

wherein inhibition of said biochemical pathway  
5 inhibits the growth of said bacterium.

6. The method of claim 5, wherein said gene corresponds to SEQ ID NO. 60 and wherein said compound has the structure:

10



wherein

R, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are independently H, alkyl (C<sub>1</sub>-C<sub>5</sub>), or  
15 halogen;

R<sup>4</sup> is H, alkyl (C<sub>1</sub>-C<sub>5</sub>), halogen, SH, or S-alkyl (C<sub>1</sub>-C<sub>3</sub>);

R<sup>5</sup> is H, alkyl (C<sup>1</sup>-C<sup>5</sup>), or aryl (C<sub>6</sub>-C<sub>10</sub>);

R<sup>6</sup> is CH<sub>2</sub>NH<sub>2</sub>, alkyl (C<sub>1</sub>-C<sub>4</sub>), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, or aryl  
20 (C<sub>6</sub>-C<sub>10</sub>);

or

R<sup>5</sup> and R<sup>6</sup> together are -C(R<sup>7</sup>)=C(R<sup>8</sup>)-C(R<sup>9</sup>)=C(R<sup>10</sup>)-, -N=C(R<sup>8</sup>)-C(R<sup>9</sup>)=C(R<sup>10</sup>)-, -C(R<sup>7</sup>)=N-C(R<sup>9</sup>)=C(R<sup>10</sup>)-, -C(R<sup>7</sup>)=C(R<sup>8</sup>)-N=C(R<sup>10</sup>)-, or -C(R<sup>7</sup>)=C(R<sup>8</sup>)-C(R<sup>9</sup>)=N-;

wherein  $R^7$ ,  $R^8$ ,  $R^9$ , and  $R^{10}$  are independently H, alkyl ( $C_1$ - $C_5$ ), halogen, fluoroalkyl ( $C_1$ - $C_5$ );

or

$R^7$  and  $R^8$  together are  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ .

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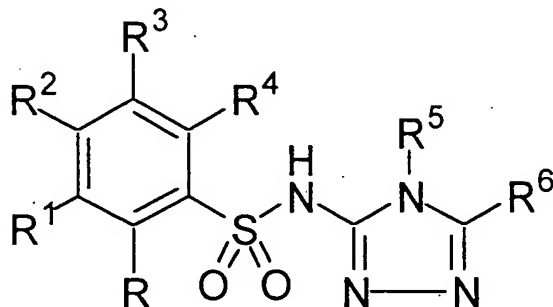
7. The method of claim 4 or 5 wherein said antibacterial agent inhibits the activity of an expression product of a bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105.

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8. A method of prophylactic treatment of a mammal, comprising administering to a mammal at risk of a bacterial infection a compound active against a bacterial gene selected from the group consisting of the genes  
15 corresponding to SEQ ID NO. 1-105.

9. The method of claim 8, wherein said gene corresponds to SEQ ID NO. 60 and wherein said compound has the structure:

20



wherein

R, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are independently H, alkyl (C<sub>1</sub>-C<sub>5</sub>), or halogen;

R<sup>4</sup> is H, alkyl (C<sub>1</sub>-C<sub>5</sub>), halogen, SH, or S-alkyl (C<sub>1</sub>-C<sub>3</sub>);

R<sup>5</sup> is H, alkyl (C<sup>1</sup>-C<sup>5</sup>), or aryl (C<sub>6</sub>-C<sub>10</sub>);

- 5 R<sup>6</sup> is CH<sub>2</sub>NH<sub>2</sub>, alkyl (C<sub>1</sub>-C<sub>4</sub>), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, or aryl (C<sub>6</sub>-C<sub>10</sub>);

or

- 10 R<sup>5</sup> and R<sup>6</sup> together are -C(R<sup>7</sup>)=C(R<sup>8</sup>)-C(R<sup>9</sup>)=C(R<sup>10</sup>)-, -N=C(R<sup>8</sup>)-C(R<sup>9</sup>)=C(R<sup>10</sup>)-, -C(R<sup>7</sup>)=N-C(R<sup>9</sup>)=C(R<sup>10</sup>)-, -C(R<sup>7</sup>)=C(R<sup>8</sup>)-N=C(R<sup>10</sup>)-, or -C(R<sup>7</sup>)=C(R<sup>8</sup>)-C(R<sup>9</sup>)=N-;

wherein R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>10</sup> are independently H, alkyl (C<sub>1</sub>-C<sub>5</sub>), halogen, fluoroalkyl (C<sub>1</sub>-C<sub>5</sub>);

or

- 15 R<sup>7</sup> and R<sup>8</sup> together are -CH=CH-CH=CH-.

10. A method of screening for an antibacterial agent,

- 20 comprising determining whether a test compound is active against a bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105.

11. A method of claim 10, comprising the steps of:

- 25 a. providing a bacterial strain having a mutant form of a gene selected from a group consisting of the genes corresponding to SEQ ID NO. 1-105, or a gene homologous

thereto, wherein said mutant form of the gene confers a growth conditional phenotype;

b. providing comparison bacteria of a bacterial strain having a normal form of said gene;

5        b. contacting bacteria of said bacterial strains with a test compound in semi-permissive growth conditions;

c. determining whether the growth of said bacteria having said mutant form of a gene is reduced in the presence of said test compound compared to the growth of said  
10 comparison bacteria.

12. A method of screening for an antibacterial agent, comprising the steps of:

a) contacting a cell expressing a polypeptide encoded  
15 by a gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105 with a test compound; and

b) determining whether the amount or level of activity of said polypeptide is altered;

wherein an alteration in said amount or level of  
20 activity of said polypeptide is indicative of a useful antibacterial agent.

13. A method of screening for an antibacterial agent, comprising the steps of:

25        a) contacting a polypeptide or a biologically active fragment thereof with a test compound, wherein said polypeptide is encoded by a gene selected from a group

consisting of the genes corresponding to SEQ ID NO. 1-105;  
and

b) determining whether said test compound binds to  
said polypeptide or said fragment;

5 wherein binding of said test compound to said  
polypeptide or said fragment is indicative of a useful  
antibacterial agent.

14. A method for evaluating an agent active on a  
10 gene selected from a group consisting of the genes  
corresponding to SEQ ID NO. 1-105, comprising the steps of:

a) contacting a sample containing an expression  
product of said gene with said agent; and

b) determining the amount or level of activity of  
15 said expression product in said sample.

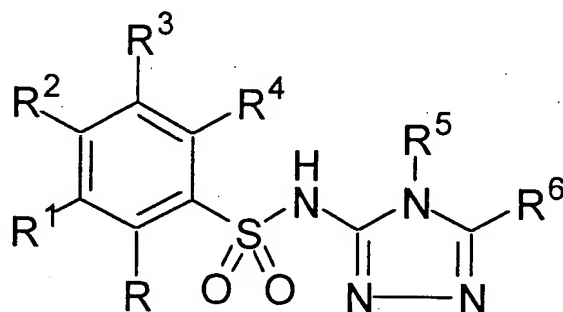
15. A method of diagnosing the presence of a  
bacterial strain having a gene selected from the group  
consisting of the genes corresponding to SEQ ID NO. 1-105,  
20 comprising probing with an oligonucleotide at least 15  
nucleotides in length which specifically hybridizes to a  
nucleotide sequence which is the same as or complementary to  
a portion of the sequence of a bacterial gene selected from  
the group consisting of the genes corresponding to SEQ ID  
25 NO. 1-105.

16. A method of diagnosing the presence of a  
bacterial strain, comprising specifically detecting the

presence of the transcriptional or translational product of a gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105.

7            11. A pharmaceutical composition comprising a  
5        pharmaceutically acceptable carrier and a compound active on a bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105.

18. The pharmaceutical composition of claim 17,  
10        wherein said bacterial gene corresponds to SEQ ID NO. 60 and wherein said compound has the structure:



15        wherein

R, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are independently H, alkyl (C<sub>1</sub>-C<sub>5</sub>), or halogen;

R<sup>4</sup> is H, alkyl (C<sub>1</sub>-C<sub>5</sub>), halogen, SH, or S-alkyl (C<sub>1</sub>-C<sub>3</sub>);

R<sup>5</sup> is H, alkyl (C<sup>1</sup>-C<sup>5</sup>), or aryl (C<sub>6</sub>-C<sub>10</sub>);

20        R<sup>6</sup> is CH<sub>2</sub>NH<sub>2</sub>, alkyl (C<sub>1</sub>-C<sub>4</sub>), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, or aryl (C<sub>6</sub>-C<sub>10</sub>);

or



$R^5$  and  $R^6$  together are  $-C(R^7)=C(R^8)-C(R^9)=C(R^{10})-$ ,  $-N=C(R^8)-C(R^9)=C(R^{10})-$ ,  $-C(R^7)=N-C(R^9)=C(R^{10})-$ ,  $-C(R^7)=C(R^8)-N=C(R^{10})-$ , or  $-C(R^7)=C(R^8)-C(R^9)=N-$ ;

wherein  $R^7$ ,  $R^8$ ,  $R^9$ , and  $R^{10}$  are independently H,  
5 alkyl ( $C_1-C_5$ ), halogen, fluoroalkyl ( $C_1-C_5$ );

or

$R^7$  and  $R^8$  together are  $-CH=CH-CH=CH-$ .

19. A method for making an antibacterial agent,  
10 comprising the steps of:

a. screening for an agent active on one of the genes  
corresponding to SEQ ID NO. 1-105 by

providing a bacterial strain having a mutant form  
of a gene selected from a group consisting of the genes  
15 corresponding to SEQ ID NO. 1-105, or a gene homologous  
thereto, wherein said mutant form of the gene confers a  
growth conditional phenotype,

providing comparison bacteria of a bacterial  
strain having a normal form of said gene,

20 contacting bacteria of said bacterial strains  
with a test compound in semi-permissive growth conditions,  
and

determining whether the growth of said bacteria  
having said mutant form of a gene is reduced in the presence  
25 of said test compound compared to the growth of said  
comparison bacteria; and

b. synthesizing said agent in an amount sufficient to provide said agent in a therapeutically effective amount to a patient.

5           20. A novel compound having antibacterial activity, wherein said antibacterial activity is against a bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105 or a product thereof.

10

          21. A purified bacterial strain expressing a mutated gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105,

          wherein said mutated gene confers a growth conditional  
15   phenotype.

          22. A recombinant bacterial cell containing an artificially inserted DNA construct comprising a DNA sequence which is the same as or complementary to a  
20   bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-3, 8, 11-20, 31-48, 59-68, 71, 76-87, 92-97, and 100-105.

          23. A recombinant cell containing an artificial-  
25   ly inserted DNA construct comprising a DNA sequence which is the same as or complementary to a portion at least 15 nucleotides in length, of a bacterial gene selected from the

group consisting of the genes corresponding to SEQ ID NO. 1-3, 8, 11-20, 31-48, 59-68, 71, 76-87, 92-97, and 100-105.

24. An oligonucleotide probe at least 15 nucleotides in length which specifically hybridizes to a nucleotide sequence which is the same as or complementary to a bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-3, 8, 11-20, 31-48, 59-68, 71, 76-87, 92-97, and 100-105.

10

25. An isolated or purified DNA sequence at least 15 nucleotides in length, comprising a nucleotide base sequence which is the same as or complementary to a portion of the base sequence of a bacterial gene corresponding to SEQ ID NO. 1-3, 8, 11-20, 31-48, 59-68, 71, 76-87, 92-97, and 100-105.

26. A DNA sequence of claim 25, the base sequence of which is the same as or complementary to the base sequence of the coding region of a bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-3, 8, 11-20, 31-48, 59-68, 71, 76-87, 92-97, and 100-105.

27. An isolated or purified DNA sequence, the base sequence of which is the same as or complementary to a bacterial gene which is homologous to a bacterial gene

selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105,

wherein the function of the expression product of said homologous gene is the same as the function of the product  
5 of said gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105.

28. An isolated or purified DNA sequence, the base sequence of which is the same as the base sequence of a  
10 mutated bacterial gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-105,

wherein expression of said DNA sequence or of said mutated bacterial gene confers a growth conditional phenotype in the absence of expression of a gene which  
15 complements said mutation.

29. A purified, enriched, or isolated polypeptide encoded by a gene selected from the group consisting of the genes corresponding to SEQ ID NO. 1-3, 8,  
20 11-20, 31-48, 59-68, 71, 76-87, 92-97, and 100-105.

30. The polypeptide of claim 29, wherein said polypeptide is expressed from a recombinant gene.